REMARKS

Claims 13-17 are pending in the application. Claims 13 and 16 have been amended to expressly state limitations implicit in the claims. Claim 16 has been further amended under 37 C.F.R. § 1.821. Claim 14 has been amended to correct an obvious error. No new matter is entered by way of these amendments.

Favorable consideration of the following comments relative to the outstanding rejections as they may apply to the pending claims is respectfully requested for the reasons that follow.

Objections to the Specification: 37 C.F.R. § 1.75(d)(1)

Specification is objected to because of lack of antecedent basis for Claim 16. The Examiner requests that Applicant either specify the provisions providing support or amend the specification to provide antecedent basis for the claimed subject matter.

Applicant directs the Examiner to the specification on page 5, lines 20-24, which provides full support for Claim 16. Accordingly, withdrawal of the objection is respectfully requested.

Sequence Listing Under 37 C.F.R. § 1.821(d)

Claim 16 is objected to under 37 C.F.R. § 1.821(d) for not including a sequence identification number for the claimed oligopeptide.

Although Applicant's response of 3 February 2003 sufficiently addresses this issue, in order to expedite prosecution of this case, the Sequence Listing has been amended to insert an identifying number for the oligopeptide. The amendment is made in adherence with 37 C.F.R. §§ 1.821-1.825. A floppy disc containing SEQUENCE ID NUMBERS 1-58 in computer readable form, and a paper copy of the sequence information accompanies this amendment. The computer readable sequence listing was prepared through use of the software program "Patent-In" provided by the PTO. The information contained in the computer readable disk is identical to that of the paper copy. This amendment contains no new matter.

Applicant submits that this amendment, the accompanying computer readable sequence listing, and the paper copy thereof serve to place this application in a condition of

adherence to the rules 37 C.F.R. §§ 1.821-1.825. Accordingly, withdrawal of the objection is respectfully requested.

Rejections Under 35 U.S.C. § 112, first paragraph: indefiniteness

Claims 13 and 16 are rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. Specifically, Claim 13 is rejected because of alleged incongruence between a peptide of six amino acids and language referring to "amino acids 84-86 are YYW."

Applicant submits that the phrase is sufficiently clear to a person of ordinary skill in the art. The claims, when viewed in context of the disclosure, specifically recite oligopeptides derived from a contiguous sequence of HLA-B α_1 domain, where the oligopeptide includes the triad YYW for the amino acid residues corresponding to positions 84 to 86 of the HLA-B α_1 domain sequence. However, in the interests of furthering prosecution of this case and without agreeing with the rejection, Applicant has rephrased the claim to expressly state the compound implicit in the prior filed claim. Applicant respectfully requests withdrawal of the rejection.

Claim 13 also stands rejected for indefiniteness regarding the phrase "species analog thereof." In the interests of furthering the prosecution of this case, and without agreeing with the Examiner's stated rejection, Applicant has deleted this phrase from the claims. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 16 is rejected for indefiniteness because of the alleged incongruence between the size of the peptides claimed in Claim 15 and Claim 16. In response, Applicant has amended the claim to expressly state subject matter implicit in the prior filed claim. Accordingly, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, second paragraph: enablement

Claims 13, 14, 16, and 17 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Applicant traverses the rejection.

The thrust of the rejection appears to be that use of the transitional phrase "comprising" encompasses numerous peptide sequence variations, including presence of additional sequences, and that peptide *function* is unpredictably affected by nature of these variations. The instant claims, however, are directed to compounds (*i.e.*, oligopeptides). Claim 13 recites that the oligopeptide is from the HLA-B α_1 domain, the sequences of which

are well known and well defined. Claim 14 recites oligopeptides in which each amino acid residue of the peptide is clearly delineated and are not unknown variants. Methods for synthesizing these peptides, either chemically or recombinantly, are well known in the art. Additional amino acid residues may be added to the claimed oligopeptides, and still comply with the enablement requirement since they can be readily made and used without undue experimentation given the knowledge of peptide synthesis and the guidance provided in the specification regarding their use.

Even if assuming, *arguendo*, that function was an issue, it is also submitted that the claimed oligopeptides with the triad YYW and additional residues outside of the claimed sequence are fully enabled. It is well known that many peptides, particularly those from protein-protein interaction domains, maintain biological activity even when placed in the context of different surrounding sequences. One such example is signal sequences, which function in trafficking proteins across cell membranes. Signal sequences may be placed with many different sequences and maintain their membrane translocating function (see, *e.g.*, Exhibit A: Lemay, G. et al., "Fusion of a Cleavable Signal Peptide to the Ectodomain of Neural Endopeptidase (EC 3.4.24.11) Results in the Secretion of an Active Enzyme in COS-1 Cells," *J. Biol. Chem.* 264(26):15620-15623 (1989; Exhibit B: Hall, J. et al., "Eukaryotic and Prokaryotic Signal Peptides Direct Secretion of a Bacterial Endoglucanase by Mammalian Cells," *J. Biol. Chem.* 265(32):19996-19999 (1990)). A second example is transcriptional activation domains, used with success in protein-protein interaction screens. The transcriptional activation domain remains active even though fused to a host of different sequences (see, *e.g.*, Exhibit C: Fields, S and Song, O., *Nature* 340(6230):245-246 (1989)). These examples show that protein domains remain bioactive in contexts different from that found in nature, and the Examiner has not provided any evidence as to why the peptide of Claim 13 from the HLA-B α_1 domain or the specifically disclosed peptides of Claim 14 would lose biological activity when attached or extended with other chemical residues.

Furthermore, knowledge of the physical structure of HLA-B molecule (see Exhibits D, E, and Fdescribed below) and the biological activities provided in the disclosure gives sufficient guidance as to the regions of HLA-B α_1 domain that can tolerate modifications, as pointed out in the specification on column 5, lines 66 through column 6, line 17.

Moreover, Applicant's position is amply supported by the working examples in the specification of bioactive oligopeptides *comprising* the recited structures. For example,

claimed oligopeptides conjugated to biotin or polylysine is biologically active in tests for inhibition of cytotoxic T lymphocytes (column 12, line 58 to column 13, line 4).

Given that the claimed oligopeptide is part of a recognized protein domain HLA-B α_1, and in view of the working embodiments provided in the disclosure, Applicant submits that the Examiner has not provided sufficient objective rationale to doubt that the oligopeptides would not function as described in the specification.

The cited references of Mikayama et al., *Proc. Natl. Acad. Sci. USA* 90:10056-10060 (1996); Lazar et al., *Mol. Cell Biol.* 8:1247-1252 (1988); Bowie et al., *Science* 247 1306-1310 (1990); and Burgess, W.H. et al., *J. Cell Biol.* 111:2129-2138 (1990) are not germane to the present claims since the references relate to amino acid sequences unrelated to the HLA-α_1 domain, a region with well understood physical and biological properties. A blanket conclusion extrapolated from not particularly relevant art does not meet the legal standard to show non-enablement.

In view of the foregoing, Applicant submits that the scope of enablement is commensurate with the scope of the claims. Accordingly, Applicant requests withdrawal of the rejection under 35 U.S.C. § 112, second paragraph for lack of enablement.

- **Rejections Under 35 U.S.C. § 112, first paragraph: written description**

Claims 13, 14, 16 and 17 are rejected under 35 U.S.C. § 112, first paragraph for lack of written description. Applicant traverses the rejection.

The essential features of the claims are the claimed oligopeptides, and the Examiner acknowledges that Applicant has sufficiently described features essential to the operation and function of the claimed sequences. The Examiner, however, extends the written description requirement to elements not part of the claims because of the transition term "comprising."

Determining what constitutes a representative number of species sufficient to support written description of a genus depends on whether one skilled in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Written description may be satisfied by recitation of a structure, formula, chemical name, or physical properties. See University of California v., Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997). Information that is well known in the art need not be described in detail in the specification to satisfy the written description requirement. See M.P.E.P § 2163(II)(A)(2).

HLA-B is a specific allele of the human Major Histocompatability Complex (MHC) Class I antigen. The α chain, involved in forming the peptide-binding cleft of the MHC complex, is composed typically of α_1, α_2 and α_3 domains. Sequences of the HLA-B α_1 domain were well known in the art at the priority date of this application, and various HLA-B variants (*i.e.*, serotypes) had been sequenced and analyzed. Moreover, the crystal structures of both HLA-A and HLA-B had clearly established the structural motifs, including the α_1 domain, involved in the function of the HLA molecule (see Exhibit D: Madde, D.R. et al., "The structure of HLA-B-27 reveals nonamer self-peptides bound in an extended conformation," *Nature* 353:621-325 (1991); Exhibit E: Bjorkman, P.J. et al., "The foreign antigen binding site and T cell recognition regions of class I histocompatability antigens," *Nature* 329:512-518 (1987); Exhibit F: Bjorkman, P.J. et al., "The foreign antigen binding site and T cell recognition regions of class I histocompatibility antigens," Nature 329:512-518 (1987)). Thus, HLA-B α_1 domain was understood and comprehended in the art by its structure, chemical name, and sequence such that attributes common to the domain were well known in the art. The disclosure provides specific structural descriptions of the HLA-B α_1 domain and the associated bioactivity of the claimed peptides. In these cases, the Synopsis of Application of Interim Written Description Guidelines (http://www.uspto.gov/web/menu/written.pdf) suggests that the written description is satisfied even when encompassing unrecited elements (see figure "Written Description Original Claims - - Decision Tree- - ").

It is further submitted that the decision in University of California v. Eli Lilly and Co. does not support the rejection. In University of California v., Eli Lilly and Co., the patentee attempted to assert a claim directed to a cDNA encoding vertebrate insulin against an infringer manufacturing human insulin. The patentee disclosed only the sequence of rat insulin cDNA but did not disclose any specific human insulin cDNA sequences. Nothing was known of the human insulin cDNA sequence. The facts of University of California v., Eli Lilly and Co. contrast with the instant disclosure, which makes numerous references to human HLA-B α_1 domain sequences, in addition to reciting the specific sequences of the claimed oligopeptides (*e.g.*, Claim 14).

In view of the foregoing, Applicant submits that the disclosure complies with the written description requirement. Accordingly, withdrawal of the rejection under 35 U.S.C. § 112, first paragraph for lack of written description is respectfully requested.

CONCLUSIONS

Applicant submits that the pending claims satisfy all the requirements of patentability and are in condition for allowance. An early notification of the same is kindly solicited. If upon review, the Examiner feels there are additional outstanding issues, the Examiner is invited to direct any calls in connection with this application to the undersigned at (415) 781-1989.

No fees beyond those included with the Amendment are believed due. However, the Commissioner is authorized to charge any additional required fees, or credit any overpayment, to Dorsey & Whitney LLP Deposit Account No. 50-2319 (Order No. A-61008/465840-00078/TAL/CYO).

Respectfully submitted,

DORSEY & WHITNEY, LLP

Dated: November 20, 2003

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